SURVIVING ANTHRAX

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REACTOGENIC VACCINE?

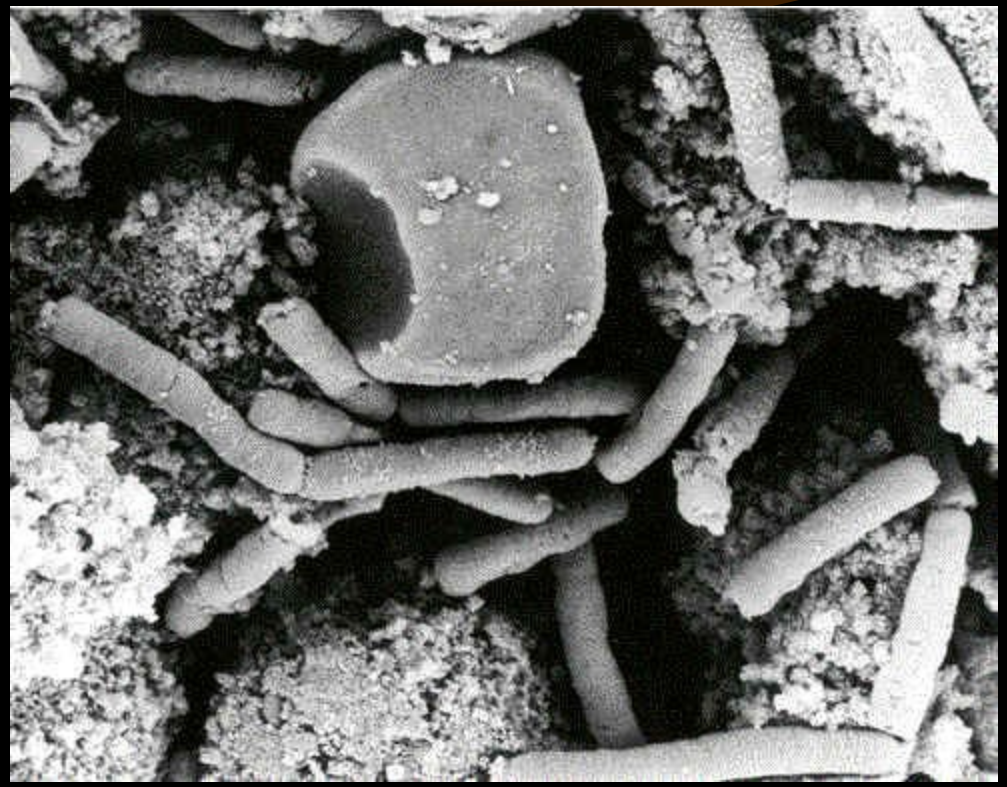
“Occasional fever may result. A nodule may be palpable at the injection site for a few weeks. Sterile abscesses and SC atrophy may occur [10 cases/million doses]. Other adverse reactions include erythema, boggy edema, pruritis, lymphadenopathy and induration surrounding the injection site, pain and tenderness. Malaise, generalized aches and pains, headaches, flushing, pruritis, tachycardia, hypotension, anaphylaxis, and neurological complications can result. Arthus-type hypersensitivity

BACKGROUND

- *Bacillus anthracis*: gram-positive bacteria, forms long-living, durable spores
- Global distribution
- Disease syndromes:
  - Cutaneous: 5-20% case-fatality rate
  - Gastrointestinal: 25-60% fatality rate
  - Inhalational: approaches 100% fatality rate

Robert Koch's original micrographs of anthrax bacillus.

Bacillus anthracis Gram stain



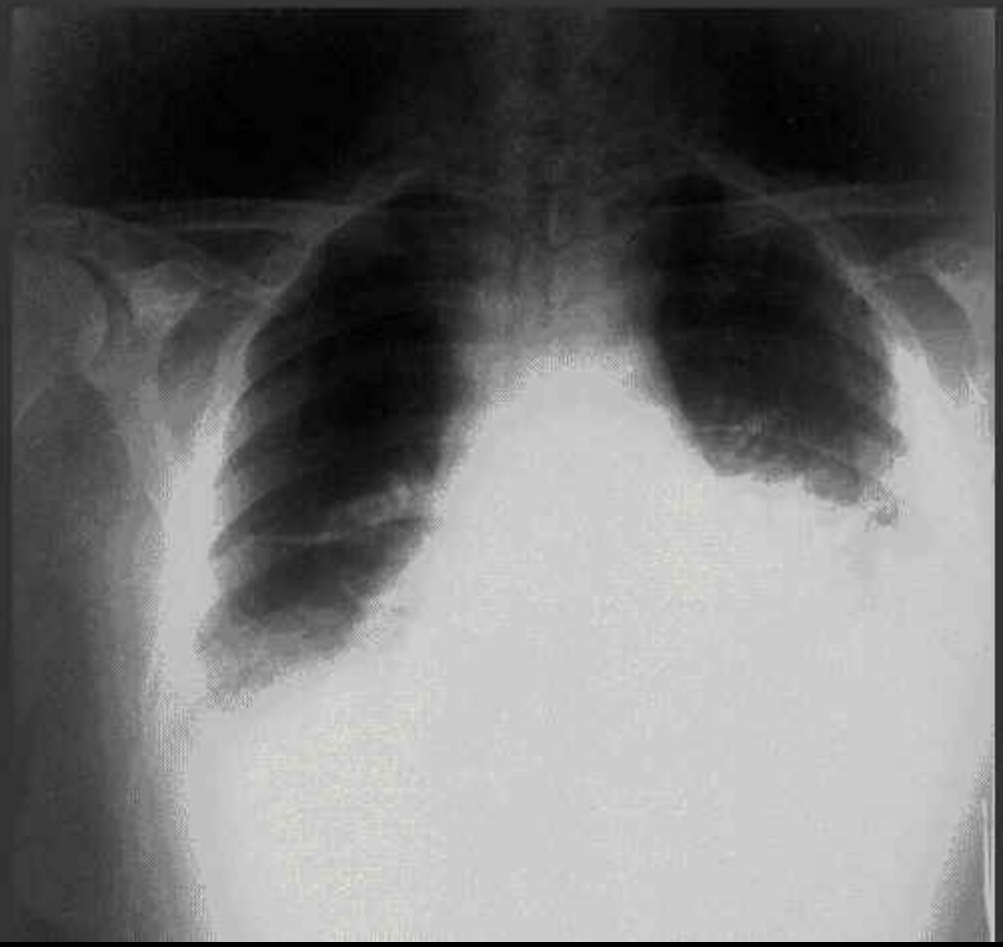
PATHOGENESIS

- Produces three important toxins:
  - Protective antigen (a binding protein which combines with one of the two factors below to produce disease)
  - Lethal factor (a metalloprotease)
  - Edema factor (adenylate cyclase)
- Produces massive and overwhelming tissue necrosis and edema

MEDICAL CONSEQUENCES OF ANTHRAX

- Anthrax is deadly - - it is 89% - 98% lethal to unvaccinated, untreated persons
- Inhalational anthrax:
  - Incubation: 1 to 6 days
  - Syndrome: abrupt respiratory distress-”flu-like”, improvement within 2-4 days, followed by shock, massive edema, hemorrhage and death 24-36 hours later

Chest radiograph showing widened mediastinum due to inhalation anthrax.
(1961)



Hemorrhagic meningitis due to inhalation anthrax.
(1966)

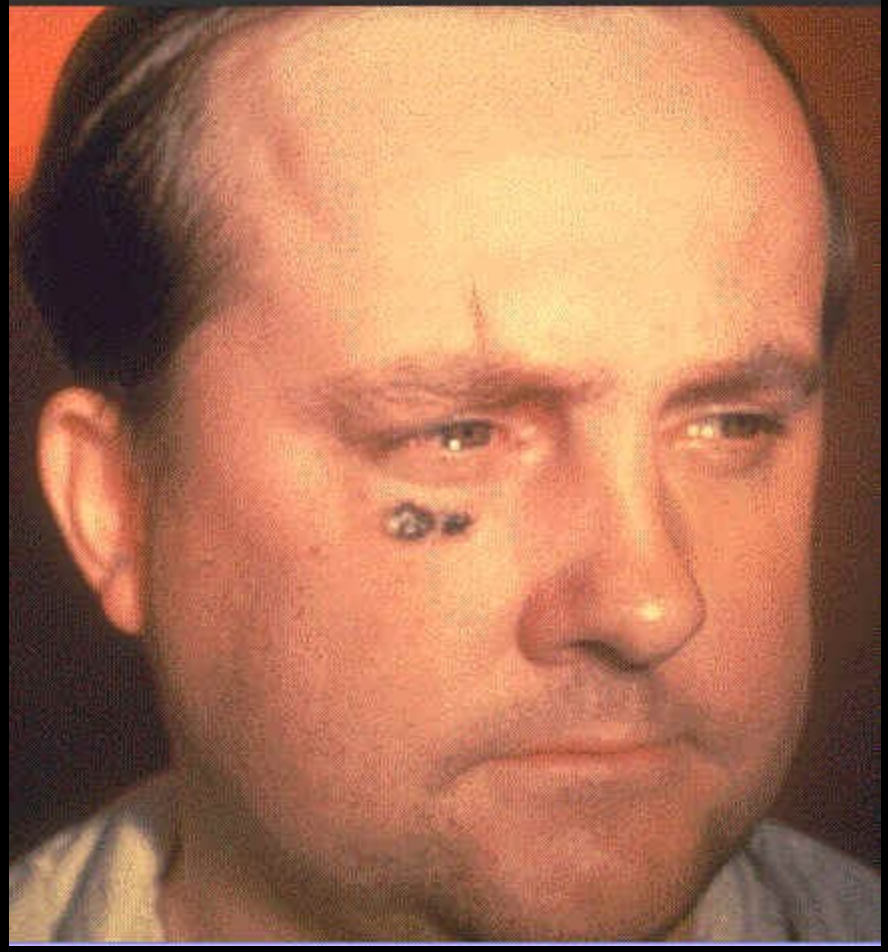
THE ISSUE

- Biological warfare is a grave and real threat to U.S. Armed Forces
- Biological terrorism is a real threat to the U.S.
- Only practical means of surviving is by pre-exposure vaccination
- The Fifth and Sixth Plagues described in the Bible

BIBLICAL CONTEXT

- “If you refuse to let them go and continue to hold them back, the hand of the Lord will bring a terrible plague on your livestock in the field” Exodus 9:2
- “It will become fine dust over the whole land of Egypt, and festering boils will break out on men and animals throughout the land” Exodus 9:10

Anthrax skin lesion on face of man.
(date unknown)



WHAT IS THE THREAT?

- Iraqi admissions to the United Nations
  - biologic weapons during Gulf War 1991
- Soviet BioWarfare Program
  - Sverdlovsk, Russia 1979
  - Accidental release of spores from a “military laboratory” - - 66 human cases occurred - - some 6 weeks later
- Domestic bioterrorism incidents

LIKELY EXPOSURE

- **Most likely:** As part of response team to a bioterroristic event
- **Next likely:** As part of other “nation on nation” collateral exposure
- **Least likely:** Directed deliberate hit on US forces

MOTIVATION

- Getting Attention
- Economic terrorism (destroy foods, livestock)
- Millenialism (new dawn after cleansing apocalypse)
- Revenge and creation of chaos
- Mimicking God
- Aura of Science and Technology
- Copycats

ATTEMPTS TO DATE - CIVILAIN

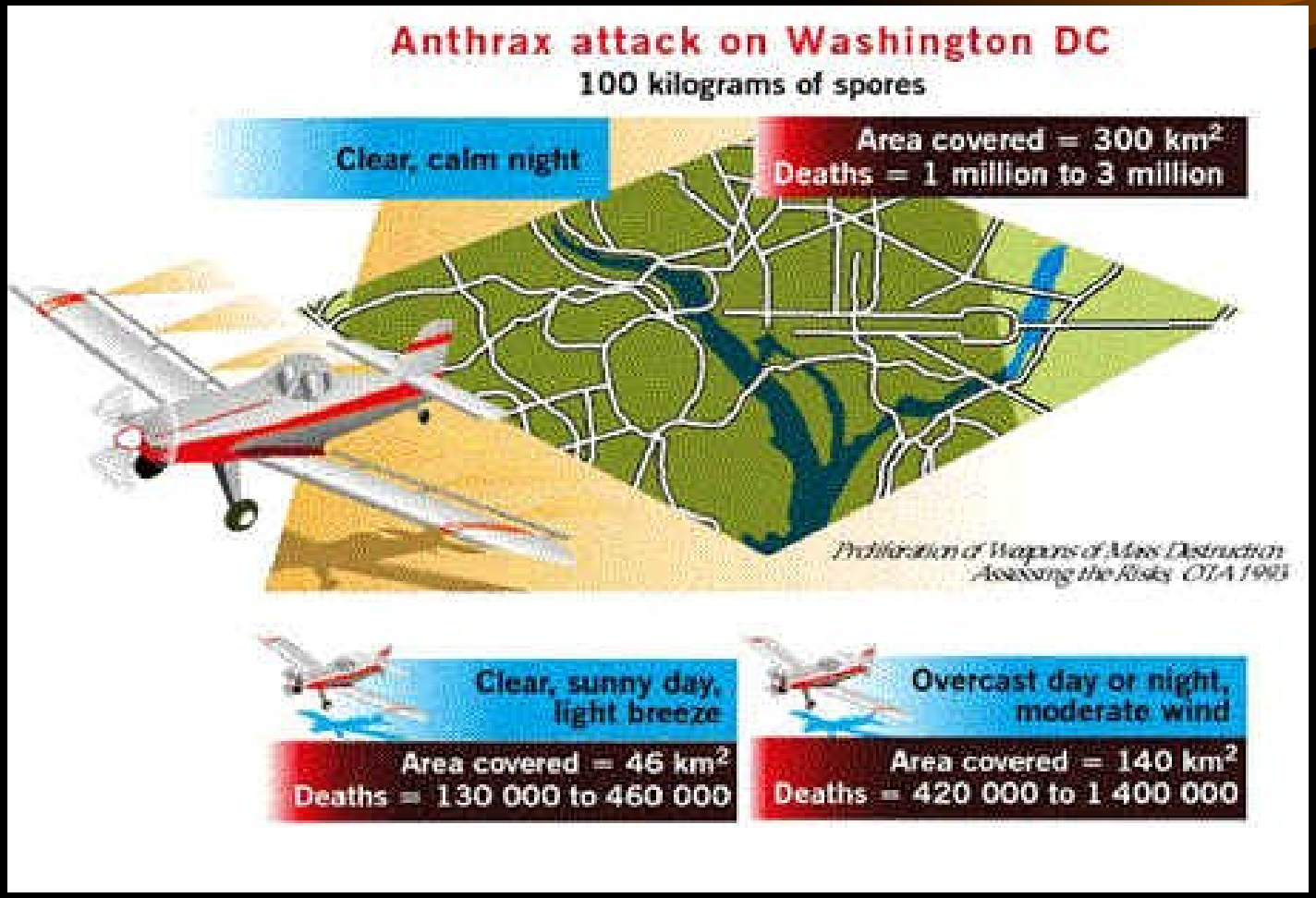
- Numerous hoax incidents
- Botched attempts
- Intercepted attempts

ANTHRAX ATTEMPTS IN THE US (1992-1999) *[Stern, EID, 1999]*

	1992	1997	1998
No. incidents	1	1	37
No. persons affected	20	100	5,529
No. decon or quar.	20	30	1,202
Target multiple	home	home	
Motivator multiple	malicious	anti-semitic	
Technique multiple	splattering	mail	
Response perimeter	perimeter sealed	perimeter sealed	sealed

ESTIMATED DANGER

- WHO reported scenario:
  - 3 days after the release of 50 kg of anthrax spores along a 2 km line upwind of a city of 500,000:
    - 125,000 infections would result
    - at least 95,000 deaths


Anthrax attack on Washington DC
100 kilograms of spores
Clear, calm night
Area covered = 300 km²
Deaths = 1 million to 3 million
Proliferation of Weapons of Mass Destruction
Assessing the Risks OTA 1993
Clear, sunny day, light breeze
Area covered = 46 km²
Deaths = 130 000 to 460 000
Overcast day or night, moderate wind
Area covered = 140 km²
Deaths = 420 000 to 1 400 000

ANTIBIOTIC PROPHYLAXIS

- Possible to provide antibiotic prophylaxis *IF* appropriate antibiotics are started immediately, along with the initial immunization series
- High dose antibiotics for 30-60 (?) days would be required in order for *some* to survive

ANTIBIOTIC PROPHYLAXIS, continued

- Penicillin and doxycycline approved for treatment of anthrax
- No FDA-approved regimens for post-exposure prophylaxis
- NOT effective against the vegetative, spore form
- Russian outbreak: suggests that lethal amounts of spores may have persisted up to 43 days after exposure (TCN allegedly used ? duration, timing)

ANTIBIOTIC PROPHYLAXIS, continued

- Macaque Studies (receiving 240,000 - 560,000 spores by inhalation)
  - 70%, 90%, and 80% survived when treated for 30 days with penicillin, doxy, or cipro; respectively (n= 10 each group)
  - deaths occurred 6 days - 28 days after discontinuing antibiotics)
  - may be able to stop antibiotics after 3 doses of vaccine (i.e. after 30 days)

ANTHRAX VACCINE

- Toxoid vaccine - - NO live organisms!
- Formaldehyde inactivated, sterile filtrate of a toxigenic, nonencapsulated strain (V770-NP1-R)
- Principal component: *Protective antigen* (toxin subunit)
- Aluminum adjuvant (2.4 mg/0.5 mL)
- Administered subcutaneously at 0, 2, 4 weeks and 6, 12, and 18 months, and annual boosters
- Lot-release criteria: potency, sterility, purity, safety

MANUFACTURING HISTORY

- FDA licensed product since 1970
- Safety and efficacy reaffirmed by an FDA advisory panel in 1985 (Fed Reg 1985;50:51002-117)
- Originally manufactured by Michigan Department of Public Health
- Renamed Michigan Biologics Products Institute in 1995
- Sold to BioPort Corporation, 1998

CONTRAINDICATIONS TO VACCINE

- Hypersensitivity/anaphylactoid reaction to previous dose
- Neurologic, severe systemic reactions, or generalized skin disease in temporal association with vaccine
- Possibly with *severe* local reactions
- Pregnancy

VACCINE UTILIZATION

- Vaccine used by veterinarians, mill workers, laboratory workers
- 1974-1989: 68,000 doses distributed
- 1990: 268,000 doses distributed (~ 150,000 service members immunized)
- 1991-1999: > 2 million doses distributed

IND STUDY (sponsored by CDC)

- Study done to provide data for licensure
- 5 year study - 16,3450 doses administered to 6,985 subjects (9,893 initial series, 6,542 annual boosters), from 4 lots of vaccine
- Reactions:
  - 20% mild local reactions (erythema,edema, induration < 30 mm)
  - 3% moderate reactions (edema and induration 30-120 mm)
  - 1% severe local reactions (edema, induration > 120 mm)
  - > 0.06% (n=4) systemic reactions (malaise, fever, chills, nausea)

EFFICACY STUDIES

- Rhesus monkeys given an aerosol challenge:
  - 44* out of 45 vaccinated monkeys survived
  - 0 out of 14 unvaccinated monkeys survived

*the one fatality was a monkey given only 2 doses of vaccine, challenged 2 years later

EFFICACY STUDIES

- Brachman et al., Am J Pub Health 1962: 1,249 workers at 4 wool mills; placebo-controlled and unvaccinated observation group.Vaccine produced from (R1-NP strain)
- Risk by person-time of exposure to ***inhalational*** disease:
  - 5 cases among 870 unvaccinated (placebo group n=414) + (unimmunized group n=340)
  - 0 cases among 379 vaccinees

Brachman Trial, continued

- Overall 26 cases of anthrax occurred in this study:
  - 3 cases of *cutaneous* anthrax in vaccinated persons (however only received 2-3 doses of vaccine)
  - 17 cases in placebo recipients (2 cases inhalational, rest cutaneous)
  - 6 cases in unimmunized participants (3 cases inhalational, rest cutaneous)

Brachman Trial, continued

- Local and Systemic Reaction Rates in the trial:
  - 4% with moderate local reactions
  - 30% mild local reactions
  - 0.2% with systemic reactions (fever, chills, body aches, nausea)

ANTHRAX VACCINE

- Between 1957-1960 improvements were made in vaccine production:
  - selection of a strain that produces a higher fraction of PA under microaerophilic conditions
  - production of a protein-free media
  - use of aluminum hydroxide rather than aluminum potassium sulfate as an adjuvant
  - patented as anthrax vaccine adsorbed (September 28, 1965)

EFFICACY STUDIES

- CDC Study 1962-1974 (follow-up study)
  - Woolen mill workers with an ongoing risk of cutaneous and inhalational anthrax
  - 27 cases of inhalational anthrax:
    - 24 cases in unvaccinated persons
    - 3 cases in partially vaccinated (1 with 1 dose, 2 with 2 doses)
    - 0 cases in fully vaccinated persons

SAFETY STUDIES

- Existing Long-Term Safety Information
  - Ft. Detrick experiences: Peeler 1958, 1965, White 1974, Pittman 1999 (unpublished)
  - 1,590 persons have received 10,451 doses of vaccine
  - Annual survey of lab workers: surveys, testing, examination
  - No evidence of any unexpected health problems

VAERS REPORTS TO DATE

- Total VAERS forms reviewed as of 7 Jan 2000 by AVEC:
  - 620 reports
  - 488 were reports other than serious (no loss of duty > 24 hours and no hospitalization)
  - Loss of duty > 24 hours: 106 (70 due to vaccine)
  - Hospitalized: 26. Of these, 6 were judged to be certainly or probably caused by vaccine (all allergic rxn at injection site)

VAERS REPORTS, continued

(1990-1999, n=607 reports, 1,580,000 doses)

- **Local Reports**
  - injection site hypersensitivity (142)
  - injection site edema (120)
  - injection site pain (95)

No deaths have been reported

- **Systemic Reports**
  - headache (104)
  - asthenia (97)
  - arthralgia (92)
  - anaphylaxis (2)
  - cellulitis (3)
  - pneumonia (3)
  - SLE (1)
  - MS (1)
  - GBS (2)

SAFETY STUDIES

- Brachman study (1962), CDC study (1960s), Fort Detrick studies (1950s to 1990s), DoD experience to date.
- Injection site reactions:
  - up to 30% with < 3 cm local reaction
  - 1-5% with redness, swelling of 1-5 inches
  - <1% with > 5 inch reaction
- Systemic events: <1% (fever, chills, nausea, muscle aches, malaise)

FDA REVIEW

- Federal Register 1985 - Specific Product Review
- “…the safety of this product is not a major concern…”
- “The Panel recommends that the license be continued because there is substantial evidence of safety and effectiveness for this product.”

LOCAL REACTION RATE STUDY

- Study of regular Army troops stationed in Korea
- Questionnaire study after the 2nd dose of anthrax vaccine
- Data of Col. Renata Engler

LOCAL REACTION RATE STUDY

Personnel	LR>5cm	SQN	PLM	LR>12cm
Total (n=2427)	11%	38.9%	11.9%	2.6%
Korea (male) (n=1953)	8.2%	31.9%	10.8%	2.0%
Korea (females) (n=474)	22.8%	67.6%	16.2%	5.8%

All male to female comparisons significant ($p<0.001$)

ANTHRAX SIDE EFFECT PROFILE - LOCAL SIDE EFFECTS

	Army Med US Forces-Korea, Bragg, USAMRIID (surveys)	Brachman, CDC Fed Reg, Ft. Detrick (occ health)	Tripler Ctr, Ft.
Soreness, tenderness	30%	60-80%	
Pain	NK	8-19%	
Lumps, nodules (weeks)		“few”	29-89%
Redness, itching, swelling			Men < 32%
< 3 cm	5-30%	Women < 63%	
3-12 cm		1-5%	1-5%
> 12 cm		< 1%	< 1%

ANTHRAX SIDE EFFECT PROFILE - SYSTEMIC SIDE EFFECTS

	Army Forces-Korea, USAMRIID (surveys 1993-99)	Brachman, CDC Fed Reg, Ft. Detrick (occ health 1960-90's)	Tripler Ctr, US
Headache	0.5-4%		14-25%
Fever, Chills	< 0.2-0.5%	1-5%	
Rash	4%	16%	
Muscle Ache	0.5-4%	3-34%	
Joint ache	0.5-4%	12-15%	
Malaise	< 0.2-4%		6-17%
Nausea	NK	3-9%	

Anthrax Vaccine Safety

- **Vision Study, USAF School of Aerospace Medicine:**
  - **178 case subjects with vision change**
  - **1,803 controls without vision change**
  - **18% of cases vaccinated, 43% of controls vaccinated; OR = 0.30 (95% CI: 0.18, 0.52)**
  - **Vision change not associated with vaccination**

Anthrax Vaccine Safety

- **USAF Air Combat Command, Langley AFB, VA**
  - **Personnel returned within 6 months from SW Asia**
  - **1,342 vaccine recipients, 3,845 unvaccinated**
  - **No elevated relative risks by ambulatory diagnosis:**
    - Allergy, arthropathy, circulatory, dermatological, digestive, endocrine, headache/neurological, hearing, infectious/parasitic, injuries, mental health, musculoskeletal, nasal, neoplastic, ocular, reproductive, respiratory, sleep disorders, urinary, unexplained illness, $\geq$ 1 diagnosis

ANTHRAX VACCINE SAFETY

- Canadian Armed Forces Study:
  - Active monitoring
  - 547 persons
  - Results:
    - mild (< 5 cm) local reactions after 10.1% of doses
    - moderate (> 5 cm) local reactions after 0.5% of doses
    - no severe local reations
    - systemic reactions (fever, headache, etc.) in 1.5%
    - no long-term adverse effects

CURRENT ADVERSE REPORTS

- VAERS reports
- Manufacturer phase IV reports
- Michigan National Guard
- Dover AFB
- Other

COMPARING PACKAGE INSERTS

Anthrax Vaccine	DPT Vaccine
“Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies have not been performed to ascertain whether Anthrax Vaccine Adsorbed has carcinogenic action, or any effect on fertility.”	“Carcinogenesis, Mutagenesis, Impairment of Fertility: ACEL-IMUNE has not been evaluated for its carcinogenic or mutagenic potential or impairment of fertility.”

COMPARING PACKAGE INSERTS

Anthrax Vaccine	Chicken Pox Vaccine
"Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies have not been performed to ascertain whether Anthrax Vaccine Adsorbed has carcinogenic action, or any effect on fertility."	"Carcinogenesis, Mutagenesis, Impairment of Fertility: Varivax has not been evaluated for its carcinogenic or mutagenic potential, or its potential to impair fertility."

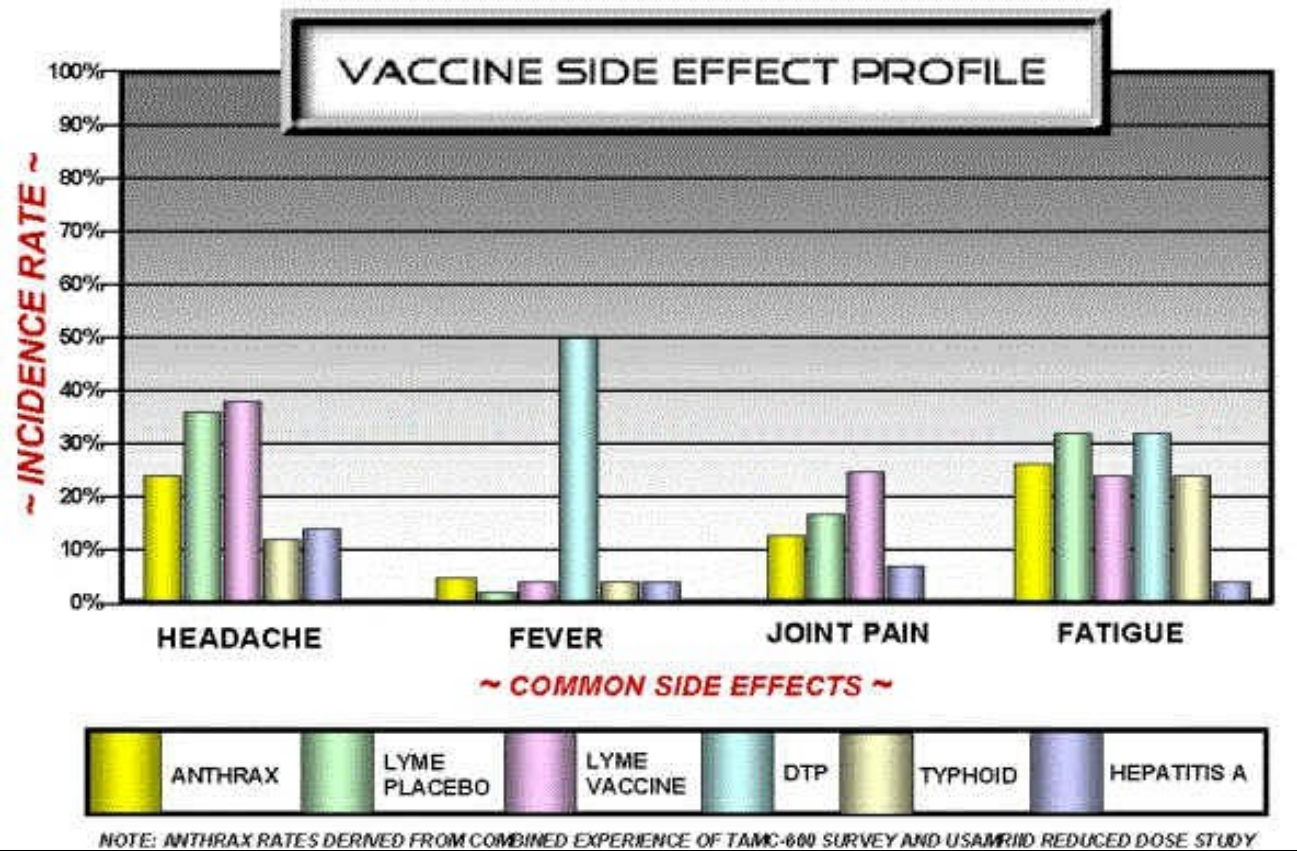
COMPARING PACKAGE INSERTS

Anthrax Vaccine

"Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies have not been performed to ascertain whether Anthrax Vaccine Adsorbed has carcinogenic action, or any effect on fertility."

Oral Polio Vaccine

"Carcinogenesis, Mutagenesis, Impairment of Fertility: Orimune has not been evaluated for its carcinogenic or mutagenic potential, or for impairment of fertility."


VACCINE SIDE EFFECT PROFILE
~ INCIDENCE RATE ~
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
HEADACHE
FEVER
JOINT PAIN
FATIGUE
~ COMMON SIDE EFFECTS ~
ANTHRAX
LYME PLACEBO
LYME VACCINE
DTP
TYPHOID
HEPATITIS A
NOTE: ANTHRAX RATES DERIVED FROM COMBINED EXPERIENCE OF TAMC-600 SURVEY AND USAMRIID REDUCED DOSE STUDY

COMPARATIVE REACTION RATES

Vaccine	Local	Systemic
Flu	30%	1-20%
HBV	22%	15%
IPV	13%	38%
Pneum	50%	5%
Td	common	few
percent		
Anthrax	30%	0.2%

CLINICAL VACCINE TRIAL

Reaction	Lyme*			Anthrax
Redness	21%			
Soreness	68%		30%	
Swelling	11%			
Joint pain	16%			
Fatigue		33%		<1%
Headache	37%			

*Lymerix clinical trial (rates reported in

CURRENT ISSUES

- Lack of Information
- Misinformation
- Disinformation
- Fear
- Media and Congressional Interest

DoD ANTHRAX POLICY

- Ordered by SECDEF on 15 Dec 97
- Phased approach:
  - Phase I: High threat areas: Kuwait, Saudi Arabia, Bahrain, Jordan, Oman, Qatar, UAE, Yemen, Israel
  - Phase II: Start 2QFY00: early deploying forces into high threat areas
  - Phase III: Remainder of Total Force

*TOTAL DOSES ADMINISTERED**

Dose CG	Army	Air Force	Navy	Marines	Total
#1	111,234	95,734	63,453	62,633	333,349
295					
#2	100,658	90,443	59,439	58,489	309,306
277					
#3	88,298	84,371	54,212	53,128	280,274
265					
#4	55,388	52,444	16,995	14,737	139,677
113					
#5	11,135	13,931	3,586	1,550	30,212
10					

VACCINE AND CAUSALITY?

- Temporal relationship is not sufficient
  - DTP and SIDS
  - Influenza vaccine and GBS
  - Hepatitis B and demyelination syndromes
- Biologic plausibility is important
- Positive and negative challenge studies
- Difficult to *disprove* rare events

ANTHRAX VACCINE ? SQUALENE

- The vaccine *does not* contain squalene
- Squalene is a cholesterol derivative - present in health food supplements, creams, suntan lotion, etc.
- It is actively being investigated as a vaccine adjuvant - - it is locally reactogenic but with no undue side effects or unusual systemic adverse events

The Little & Knudson Paper (1986)

- 27 “strains” (not defined, actually isolates) used to challenge guinea pigs who had been immunized with the current vaccine by injecting the bacilli intramuscularly .
- 9 of the isolates produced a greater than 50% mortality in the immunized animals.
- These were called “vaccine resistant” strains.

The Little & Knudson Paper, continued

- Problems:
  - only 3 injections of vaccine had been given
  - the vaccine was given IM, not SQ
  - the disease challenge was IM, not inhalational
  - guinea pigs do not have the same disease process as primates, hence it is a flawed model

ANIMAL STUDY SUMMARY

- Guinea pigs are a medically inappropriate challenge model
- The anthrax vaccine protects both rabbits and nonhuman primates against *all* anthrax strains tested in guinea pigs - - including anthrax challenge strains that kill immunized guinea pigs

VACCINE AND GULF WAR ILLNESSES

- No evidence of link between anthrax vaccine and illnesses of Persian Gulf War veterans:
  - Presidential Advisory Committee on Gulf War Veteran's Illnesses, Dec 1998
  - Institute of Medicine, 1996
  - NIH Workshop, 1994
  - Defense Science Board Task Force on Gulf War Effects, 1994
  - Hospitalization: NEJM 1996;335:1505
  - Mortality: NEJM 1996;335:1498
  - Birth Defects: NEJM 1997;336:1650

GULF WAR SYNDROME AND ANTHRAX

- Some have suggested that GWS is due to anthrax (or other) vaccines. What we know is that:
  - The mortality rate of Gulf War veterans is less than half that of the civilian population (adjusted standardized mortality ratio of 0.44)
  - Deaths due to medical causes have NOT increased
  - NO overall increase in hospitalizations or birth defects

LEARNING FROM HISTORY

- Similar fears have attended the introduction of *every* vaccine starting with Jenner and smallpox vaccine
- The vaccine is imperfect - - and always will be - - BUT it appears to be effective and safe
- The disease is lethal, once exposed - - you *will* die

LEARNING FROM HISTORY, continued

- Vaccines that are reactogenic are most likely to be viewed with suspicion
- Vaccines that are mandated by some authority, are more likely to be viewed by the populace with suspicion

WHAT'S NEXT?

- Better vaccines?
- Use in key civilian sectors
- More studies
  - IM rather than SC?
  - Decreased number of doses?
  - Decreased dose amount?
  - Gender differences?

NEW STUDIES PLANNED

- Different route of administration
- Different dosing schedules
- Dept. of the Army Anthrax Longitudinal Studies
  - hospitalizations
  - outpatient visits
  - birth registry
  - pregnancy registry

WHAT SHOULD YOU DO?

- It is a direct and lawful order designed to maintain military readiness
- Inform yourself with scientific facts, not fears and anecdotal reports
- Discuss with medical staff your concerns, possible contraindications, fears and side effects
- Report any side effects through VAERS

CONCLUSIONS

- Anthrax is the single most likely and viable biologic weapon to which US troops could be exposed
- A safe and effective vaccine is available which prevents disease and death in humans

CONCLUSIONS, continued

- The vaccine is locally reactogenic
- There is no credible evidence for a “vaccine resistant” strain of anthrax
- While the possibility of a rare unknown adverse effect occurring during large-scale use of vaccine exists, there is no evidence of this in over 30 years of use

RESOURCES

- DoD website: www.anthrax.osd.mil
- Toll-free information line: 877-GET-VACC
- Free e-mail answer service: avip@otsg.amedd.army.mil

RESOURCES, continued

- Brachman et al. Anthrax. In: Plotkin SA, Orenstein WA, eds. Vaccines, 3rd ed. WB Saunders CO; 1999:629-637.
- Friedlander AM et al. Anthrax Vaccine: Evidence for Safety and Efficacy Against Inhalational Anthrax. JAMA 1999;282:2104-2106.

WHY I CARE…

It is the soldier, not the reporter, who has given us freedom of the press.
It is the soldier, not the poet, who has given us freedom of speech.
It is the soldier, not the campus organizer, who has given us the right to demonstrate.
It is the soldier, who salutes the flag, who serves beneath the flag,
And whose coffin does the flag drape, who allows the protester to burn the flag."

--- Father Denis Edward O'Brien, USMC